Application Reviews by RFA/Genomics/GC1R-06702

REVIEW REPORT FOR CIRM RFA 12-06R GENOMICS CENTERS OF EXCELLENCE AWARDS (R)

GC1R-06702: Collaborative Center for Stem Cell Genomics

GWG Overall Center Recommendation: Tier 1
GWG Overall Final Score: 75

GWG Data Center Recommendation: Tier 1
GWG Data Center Final Score: 78

CIRM Staff Recommendation: Do not fund

Public Abstract (provided by applicant)
The Collaborative Center for Stem Cell Genomics is a full service Genomics Center dedicated to the application of innovative genomic approaches to important problems of human stem cell biology. Filled with leading experts in genomics, bioinformatics, biostatistics, computational biology, and stem cell biology from four preeminent public research institutions in California, the Center advances the science of human stem cell research, provides cutting-edge approaches to genomic data analysis, and engages Californian stem cell researchers in collaborative studies. To advance the science of human stem cell research, the Center will initiate four transformative projects: (1) develop a novel way to measure how each of millions of gene combinations affects mammalian cell development and apply this technology to stem cell research; (2) use a unique panel of embryonic stem cell lines to study their development; (3) use a single-cell approach to study stem cell self renewal; and (4) generate a single cell resource of human nerve cell gene expression pattern to improve cell replacement therapies. In addition, the Center will support 12 collaborative projects from leading Californian stem cell researchers and help them apply genomic tools in their work. The expertise and creativity of the scientists in the Center, coupled with its considerable resources, uniquely positions the Center to advance stem cell research through genomic and epigenomic analysis.

Statement of Benefit to California (provided by applicant)
The Collaborative Center for Stem Cell Genomics benefits the State of California and its citizens in 4 major ways. First, the Center applies cutting-edge genomic and bioinformatic approaches to study important questions in stem cell biology. As such, it hastens the pace of stem cell research and brings us a few step closer to reaping the medical benefits of stem cell research. Second, the research projects being pursued by the Center will create new technologies that may be used for treatment of neurological and other disorders, and identification of gene combinations that promote formation of specific tissues. Great economic benefits will be realized in California even if a fraction of the research conducted in the Center is successful. Third, the expertise found in the Center is unparalleled. The Center experts are committed to collaborating with other stem cell research groups to do the best science. When new discoveries are made, important new research questions will likely arise. Center supported projects will be in great position to compete for federal grants and private funding, leading to more research dollars coming to California. Finally, the Center's use of state-of-the-art technologies will allow us to train a new generation of researchers, technicians, and computer scientists, thus increasing the competitive edge of California. Many of the young scientists from our Center will likely become key workers in new biotech companies in the state.

Review Summary
This application for a Genomics Center of Excellence Award represents a collaboration between 4 academic and government research institutions within the state of California. Four independent Center-Initiated Projects (CIPs) have been proposed, encompassing studies ranging from novel tool development for combinatorial gene manipulation and analysis to investigations of key stem cell properties and behaviors using single cell profiling and other cutting edge approaches. The application includes a Data Coordination and Management center and a Collaborative Research Plan for supporting up to 12 projects proposed by California-based stem cell scientists.

Center Organization and Operational Plan
- The Program Director has long experience in genome research, particularly in connection with consortium projects involving cooperative collection and analysis of massive data sets.

- The Center Organization and Operational Plan is well suited to the management of a program at the proposed scale and complexity.

- The Steering Committee consists of internationally recognized experts who are well qualified for core decision making in the planned operations.

- The proposed Center builds on existing strong infrastructure in genomics and computational analysis.

- Concerns were expressed about the coordination of technologies, access and data.

- The proposal lacks an integrated plan or overall vision appropriate for a major genomics center.

- Proposed matching funds from the applicant institution were considered relatively modest.

Collaborative Research Projects

- The proposal includes a strong plan for engaging and supporting collaborative research projects at multiple levels, including design, data collection and analysis.

- Reviewers praised the plan to solicit letters of intent from investigators who may have limited experience in genomic assays and informatics, and then to assist promising applicants with development of their full proposals. In this way, the final applications will be both practical and scaled to the resources available.

- While the nominated members of the Collaborative Resource Committee reflect a strong group of established scientists, reviewers expressed concern that the named individuals represent a very limited number of California institutions.

CIP-1

The goal of this project is to develop novel tools for systematically uncovering relevant gene interaction networks that define cell fate. Specifically, the applicants propose to develop vector libraries that enable simultaneous manipulation of vast combinations of different genes within mammalian cells. These libraries will be used to identify and test new combinations of genes that may enable cell-type specific reprogramming to be achieved in vitro and in vivo.

- Reviewers admired the innovation of this approach but were uncertain of its overall feasibility for engineering cell fate, as the proposed expression system would not recapitulate differences in individual gene dosage and timing that might prove important for the correct specification of cell identity.

- The project description is written in a very vague and general way, leaving reviewers with questions about how genetic combinations would be chosen, how quantitative genetic interactions would be scored and verified, and how relevant findings from other genetic interaction studies would be incorporated.

- The approaches used to develop combinatorial vectors with barcoded contents are extremely clever and sound, but their potential to be transformative might be increased through incorporation of powerful new Cas9/CRISPR technology, or features such as inducible expression.

- The project would benefit from involvement of experts on the cell types to be derived.

- The plans to achieve transdifferentiation in vivo (Aim 4) are premature and poorly developed.

- The project leader is an expert in genetics and noncoding RNA, with an excellent track record and career on an upward trajectory.

CIP-2

The goal of this project is to elucidate the molecular mechanisms that guide the earliest fate decisions that occur during human embryogenesis. Using a unique panel of non-federal human embryonic stem cells (hESCs), the applicants propose to use single cell profiling techniques to assess transcriptional and epigenetic changes that occur as hESCs transition from pluripotency to specialized cell fates within the ectodermal, mesodermal, endodermal and extra-embryonic lineages.

- Exploring the possibility that cell types leading to conventional hESCs have already passed irreversible differentiation steps prior to derivation from blastocysts is biologically innovative and would contribute to growing knowledge of early development in humans.

More insight into these very early processes might also lead to improved hESCs or even induced pluripotent stem cells and differentiation protocols.

- While there may well differences between the novel hESCs to be studied and more conventional, established hESC lines, reviewers questioned whether significant, novel findings would result from the proposed study. It was emphasized that laboratory-specific conditions and donor genetic background can also alter gene expression and epigenetic signatures.

- The proposed analyses are largely based on observational approaches. Reviewers suggested that more meaningful conclusions could be drawn by performing side-by-side comparisons, or by supplementing these observational studies with better-defined hypotheses about causal relationships.

- The experiments are feasible and employ cutting edge approaches.

- The project leaders constitute a strong team, combining extensive experience with the study of epigenetics and the biology of early human development.

CIP-3

This project aims to apply single cell transcriptional profiling approaches to elucidate the origins of pluripotency and self-renewal during human pluripotent stem cell (hPSC) derivation. The applicants will begin by developing a pipeline of tools for implementing large scale, single cell analysis by RNA-seq. These techniques will then be applied towards characterizing the molecular stages that occur as hESC develop from the inner cell mass of blastocysts in vitro, and during the reprogramming of human primordial germ cells to embryonic germ cells.

- The proposed studies are highly innovative and tackle a novel and understudied area that could not be funded by the federal government. Insights gained would be significant, with implications both in the practical derivation and growth of human pluripotent cells and their differentiation for regenerative medicine.

- The resources and data to be developed in this project would be of considerable value for the stem cell community. Reviewers lauded the plans to make the results and methodology widely available via the Internet.

- The proposed experiments are highly feasible based on strong preliminary data, established methods, and the unique, existing infrastructure that is already in place for deriving hESCs from donated embryos at the applicant institution.

- The project leader, a stem cell biologist with expertise in germ line development and epigenetics, is highly qualified to carry out the proposed research. His/her skills are complemented by outstanding collaborators with knowledge of genomics, informatics, stem cell culture and RNA-seq.

- Reviewers were uncertain whether pluripotent stem cell lines from human embryonic germ cells could be readily propagated.

CIP-4

This project aims to create a resource of single cell gene expression data from the developing human brain, thereby enabling a "report card" to be developed for improving and standardizing differentiation protocols for neural cell-based therapies. Specifically, the applicants will compare profiles from primary human neural cells at various stages of early development with corresponding differentiated derivatives of human induced pluripotent cells (hiPSCs) and hESCs. Identified candidate factors will be manipulated and assessed for their ability to improve the correlation between the various compared populations, and their ability to improve differentiation and functionality of hiPSC-derived neural precursors upon transplantation into various animal models of disease.

- Reviewers viewed this as an outstanding project that addresses a major limitation in regenerative biology- the current lack of understanding of target cell types in vivo and how they are emulated by in vitro derived models.

- Feasibility is strongly supported by the investigators' established resources for accessing primary tissues, prior experience with the platforms to be utilized, and demonstrated expertise in the derivation of highly specialized neuronal subtypes from iPSCs.

- The project director, a seasoned scientific leader in neuroscience and stem cell biology, is a key strength of the proposal. The research team are primarily early-career investigators but appear highly qualified.

- The timely release of data from this study should be extremely useful to the stem cell community for designing and evaluating differentiation protocols. To maximize the value of this resource, reviewers recommended inclusion of additional iPSC and hESC lines in comparisons to ensure discoveries will be applicable to a wide range of cell lines, and to account for variability due to genetic background of donor cells. Frequent interactions with other stem cell researchers will also be important for validating and confirming findings.

Data Coordination and Management

- The proposed Data Coordination and Management (DC&M) center will leverage existing, state of the art resources and should prove fully capable of delivering the stated goals of the proposal.

- Reviewers expressed some concerns that the proposed DC&M team lacked adequate experience with handling data from cutting-edge human DNA sequencing technologies.

- While some reviewers were uncertain of the timeline in which the proposed DC&M center would become proficient in the specific and unique challenges of the human genome, they believed that the underlying quality and track record of the individual DC&M leaders is such that extremely innovative approaches and solutions would emerge.

- The proposed staffing and budget for data management are appropriate for coordination of all genomics data generated through activities of the stem cell genomics center, including collaborative projects.
